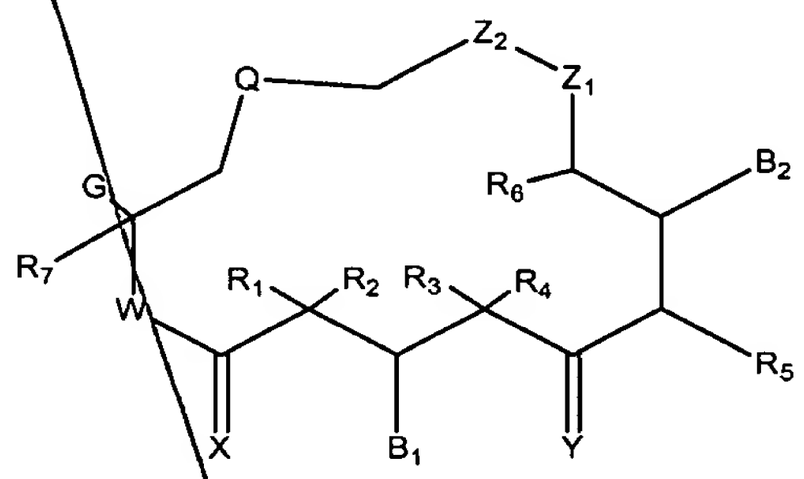
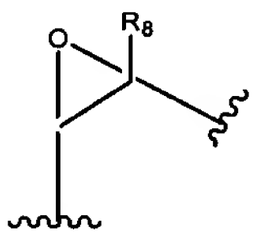
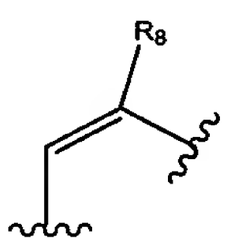
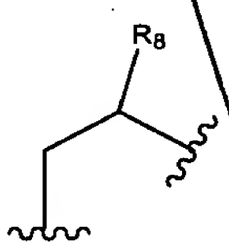
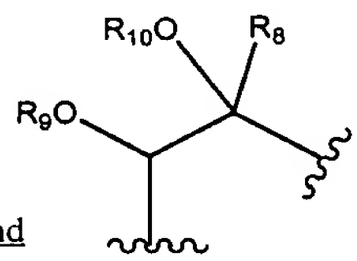
1. (Fourth amendment) A compound of the formula:



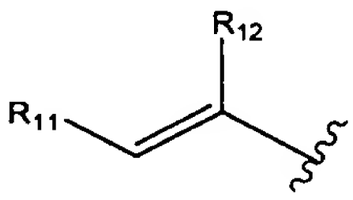
V

wherein:

Q is selected from the group consisting of:




and


G is selected from the group consisting of alkyl; substituted alkyl; substituted aryl; a 4 to 7 membered monocyclic, 7 to 11 membered bicyclic, or 10 to 15 membered tricyclic saturated or unsaturated ring system having between 1 and 3 heteroatoms selected from nitrogen, oxygen, and sulfur;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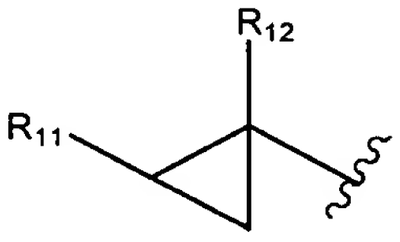
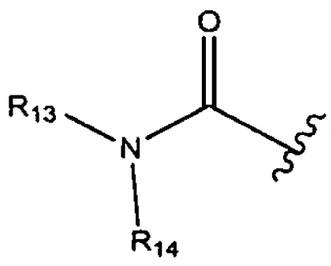

, and


W is O or NR_{15};

X is O or H, H;

Y is selected from the group consisting of O; H, OR_{16}; OR_{17}, OR_{17}; NOR_{18}; H, NOR_{19}; H, $NR_{20}R_{21}$; H, H; and CHR_{22}; wherein OR_{17}, OR_{17} can be a cyclic ketal;

Z_1 and Z_2 are independently CH_2;

B_1 and B_2 are independently selected from the group consisting of OR_{24}, $OCOR_{25}$, and O-C(=O)-$NR_{26}R_{27}$, and when B_1 is OH and Y is OH, H, they can form a six-membered ring ketal or acetal;

R_1, R_2, R_3, R_4, R_5, R_7, R_{13}, R_{14}, R_{18}, R_{19}, R_{20}, R_{21}, R_{22}, R_{26} and R_{27} are selected from the group consisting of H, alkyl, substituted alkyl, and aryl, and when R_1 and R_2 are alkyl can be joined to form a cycloalkyl, and when R_3 and R_4 are alkyl can be joined to form a cycloalkyl;

R_6 is methyl;

R_9, R_{10}, R_{16}, R_{17}, R_{24}, R_{25} and R_{31} are selected from the group consisting of H, alkyl, and substituted alkyl;

R_{11}, R_{12}, R_{28}, R_{30}, R_{32}, and R_{33} are selected from the group consisting of H; alkyl; substituted alkyl; aryl; substituted aryl; cycloalkyl containing 1 to 3 rings and 3 to 7 carbons per ring which may be further fused with an unsaturated C_3-C_7 carbocyclic ring; and a 4 to 7 membered monocyclic, 7 to 11 membered bicyclic, or 10 to 15 membered tricyclic saturated or unsaturated ring system having between 1 and 3 heteroatoms selected from nitrogen, oxygen, and sulfur;

R_8 is hydrogen or methyl;

R_{15}, R_{23} and R_{29} are selected from the group consisting of H; alkyl; substituted alkyl; aryl; substituted aryl; cycloalkyl containing 1 to 3 rings and 3 to 7 carbons per ring which may be further fused with an unsaturated C_3-C_7 carbocyclic ring; a 4 to 7 membered monocyclic, 7 to 11 membered bicyclic, or 10 to 15 membered tricyclic saturated or unsaturated ring system having between 1 and 3 heteroatoms selected from nitrogen, oxygen, and sulfur; $R_{32}C{=}O$; $R_{33}SO_2$; hydroxy; O-alkyl or O-substituted alkyl;

or pharmaceutically acceptable salts thereof, hydrates, solvates or geometric, optical or steroisomers thereof;

with the proviso that compounds wherein

W and X are both O; and

R_1, R_2 and R_7 are H; and

R_3, R_4 and R_6 are methyl; and

R_8 is H or methyl; and

G is 1-methyl-2-(substituted-4-thiazolyl)ethenyl; and

Q is as defined above

are excluded.

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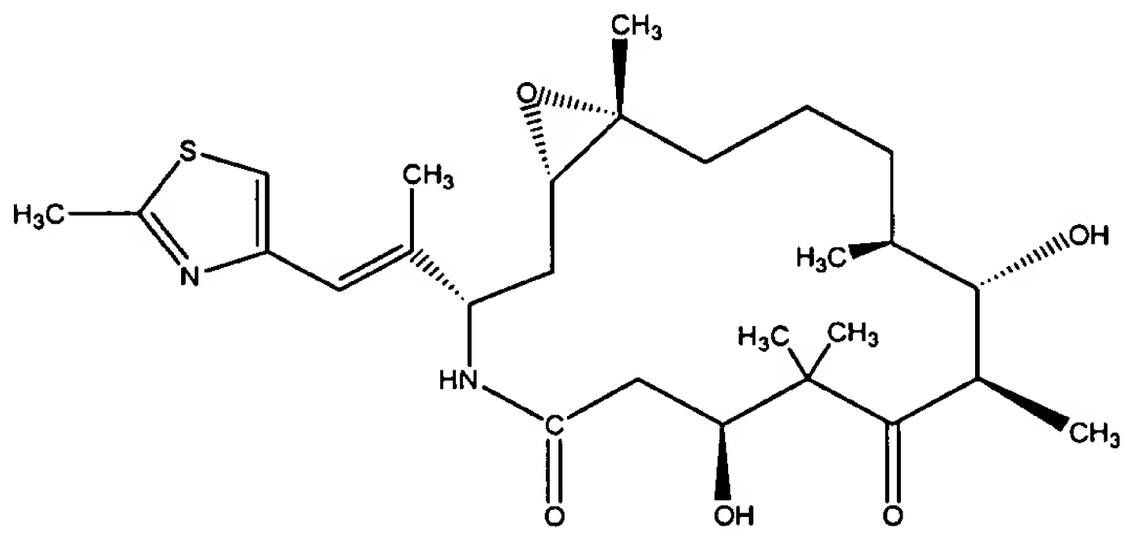
4. (Amended) A method of treating breast cancer, ovarian cancer, colon cancer, head and neck cancer, lung cancer, gynecological cancers, brain cancer, germ cell cancer, urothelial cancer, esophageal cancer, prostrate cancer, bladder cancer, or pancreatic cancer in a patient in need

of said treatment which comprises ~~administering~~ to said patient a therapeutically effective amount of a compound of claim 1.

~~6.~~ (Amended) A method of treating breast cancer, ovarian cancer, colon cancer, head and neck cancer, lung cancer, gynecological cancers, brain cancer, germ cell cancer, urothelial cancer, esophageal cancer, prostrate cancer, bladder cancer, or pancreatic cancer in a patient in need of said treatment which comprises administering to said patient a therapeutically effective amount of a compound of claim 2.

~~11.~~ (Amended) A method of treating breast cancer, ovarian cancer, colon cancer, head and neck cancer, lung cancer, gynecological cancers, brain cancer, germ cell cancer, urothelial cancer, esophageal cancer, prostrate cancer, bladder cancer, or pancreatic cancer in a patient in need of said treatment which comprises administering to said patient a therapeutically effective amount of a compound of claim 3.

~~14.~~ A compound having the formula:



or a pharmaceutically acceptable salt, hydrate, solvate, geometrical isomer, optical isomer or stereoisomer thereof.

~~15.~~ (Amended) A method of treating breast cancer, ovarian cancer, colon cancer, head and neck cancer, lung cancer, gynecological cancers, brain cancer, germ cell cancer, urothelial cancer, esophageal cancer, prostrate cancer, bladder cancer, or pancreatic cancer in a patient in need of said treatment which comprises administering to said patient a therapeutically effective amount of a compound of claim ~~14~~ 8.

17 ~~23.~~ (Amended) A method of treating breast cancer, ovarian cancer, colon cancer, head and neck cancer, lung cancer, gynecological cancers, brain cancer, germ cell cancer, urothelial cancer, esophageal cancer, prostrate cancer, bladder cancer, or pancreatic cancer in a patient in need of said treatment which comprises administering to said patient a therapeutically effective amount of a compound of claim ~~19~~. 13

E7 amd E6

19 ~~25.~~ (Amended) A method of treating breast cancer, ovarian cancer, colon cancer, head and neck cancer, lung cancer, gynecological cancers, brain cancer, germ cell cancer, urothelial cancer, esophageal cancer, prostrate cancer, bladder cancer, or pancreatic cancer in a patient in need of said treatment which comprises administering to said patient a therapeutically effective amount of a compound of claim ~~20~~. 14

E8 amd E7

21 ~~27.~~ (Amended) A method of treating breast cancer, ovarian cancer, colon cancer, head and neck cancer, lung cancer, gynecological cancers, brain cancer, germ cell cancer, urothelial cancer, esophageal cancer, prostrate cancer, bladder cancer, or pancreatic cancer in a patient in need of said treatment which comprises administering to said patient a therapeutically effective amount of a compound of claim ~~21~~. 15

E9 amd E8

23 ~~29.~~ (Amended) A method of treating breast cancer, ovarian cancer, colon cancer, head and neck cancer, lung cancer, gynecological cancers, brain cancer, germ cell cancer, urothelial cancer, esophageal cancer, prostrate cancer, bladder cancer, or pancreatic cancer in a patient in need of said treatment which comprises administering to said patient a therapeutically effective amount of a compound of claim ~~22~~. 16

E10 amd E9

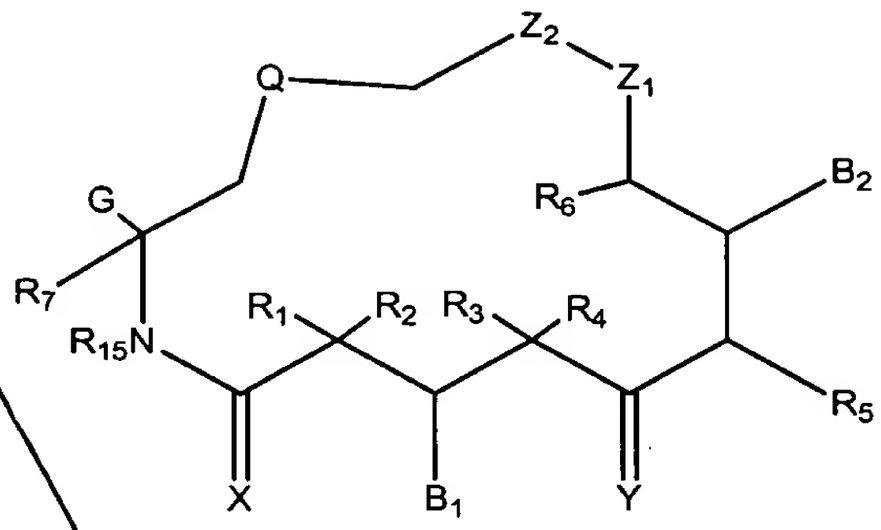
Please add the following new claim:

~~53~~ 59. (New) A compound of the formula:

E10 amd E11

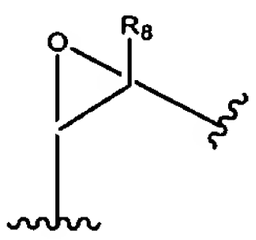
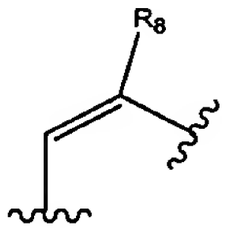
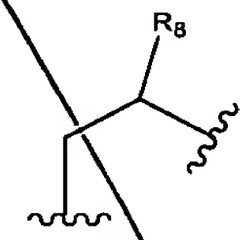
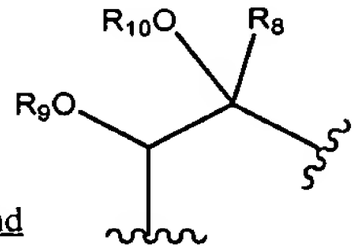
82

E

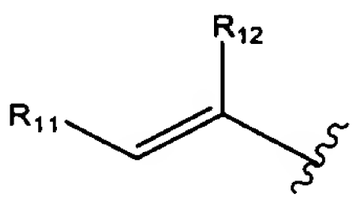


wherein:

Q is selected from the group consisting of:




and


G is selected from the group consisting of alkyl; substituted alkyl; substituted aryl; a 4 to 7 membered monocyclic, 7 to 11 membered bicyclic, or 10 to 15 membered tricyclic saturated or unsaturated ring system having between 1 and 3 heteroatoms selected from nitrogen, oxygen, and sulfur;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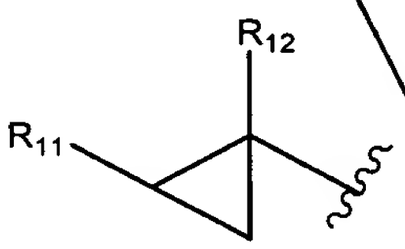
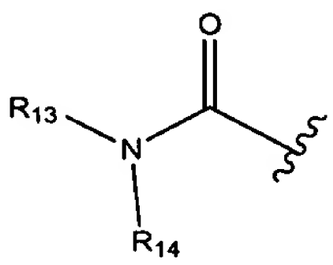

, and


X is O or H, H;

Y is selected from the group consisting of O; H, OR_{16}; OR_{17}, OR_{17}; NOR_{18}; H, NOR_{19}; H, $NR_{20}R_{21}$; H, H; and CHR_{22}; wherein OR_{17}, OR_{17} can be a cyclic ketal;

Z_1 and Z_2 are independently CH_2;

B_1 and B_2 are independently selected from the group consisting of OR_{24}, $OCOR_{25}$, and O-C(=O)-$NR_{26}R_{27}$, and when B_1 is OH and Y is OH, H, they can form a six-membered ring ketal or acetal;

R_1, R_2, R_3, R_4, R_5, R_7, R_{13}, R_{14}, R_{18}, R_{19}, R_{20}, R_{21}, R_{22}, R_{26} and R_{27} are selected from the group consisting of H, alkyl, substituted alkyl, and aryl, and when R_1 and R_2 are alkyl can be joined to form a cycloalkyl, and when R_3 and R_4 are alkyl can be joined to form a cycloalkyl;

R_6 is methyl;

R_9, R_{10}, R_{16}, R_{17}, R_{24}, R_{25} and R_{31} are selected from the group consisting of H, alkyl, and substituted alkyl;

R_{11}, R_{12}, R_{28}, R_{30}, R_{32}, and R_{33} are selected from the group consisting of H; alkyl; substituted alkyl; aryl; substituted aryl; cycloalkyl containing 1 to 3 rings and 3 to 7 carbons per ring which may be further fused with an unsaturated C_3-C_7 carbocyclic ring; and a 4 to 7 membered monocyclic, 7 to 11 membered bicyclic, or 10 to 15 membered tricyclic saturated or unsaturated ring system having between 1 and 3 heteroatoms selected from nitrogen, oxygen, and sulfur;

R_8 is hydrogen or methyl;

R_{15}, R_{23} and R_{29} are selected from the group consisting of H; alkyl; substituted alkyl; aryl; substituted aryl; cycloalkyl containing 1 to 3 rings and 3 to 7 carbons per ring which may be further fused with an unsaturated C_3-C_7 carbocyclic ring; a 4 to 7 membered monocyclic, 7 to 11 membered bicyclic, or 10 to 15 membered tricyclic saturated or unsaturated ring system having between 1 and 3 heteroatoms selected from nitrogen, oxygen, and sulfur; $R_{32}C{=}O$; $R_{33}SO_2$; hydroxy; O-alkyl or O-substituted alkyl;

or pharmaceutically acceptable salts, hydrates, solvates or geometric, optical or steroisomers thereof.

60. (New) A method of treating breast cancer, ovarian cancer, colon cancer, head and neck cancer, lung cancer, gynecological cancers, brain cancer, germ cell cancer, urothelial cancer, esophageal cancer, prostrate cancer, bladder cancer, or pancreatic cancer in a patient in need of said treatment which comprises administering to said patient a therapeutically effective amount of a compound of claim ~~59~~ 53.

61. (New) The method of claim ~~60~~ 54, wherein the cancer is cancer of the breast, ovary, or colon.

~~54~~ 62. (New) A method of treating a cancer responsive to microtubule stabilization in a patient comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of claim ~~59~~ 53.

~~63~~ 57. (New) The method of claim ~~60~~ 54, further comprising administering one or more of a additional anti-cancer agent.

~~64~~ 58. (New) The method of claim ~~63~~ 57, wherein the additional anti-cancer agent acts in a phase of the cell cycle other than the G_2-M phase.

~~65~~ 59. (New) The method of claim ~~64~~ 58, wherein the additional anti-cancer is a thymidilate synthase inhibitor, a DNA cross linking agent, a topoisomerase I or II inhibitor, a DNA alkylating agent, a ribonuclase reductase inhibitor, a cytotoxic factor, or a growth factor inhibitor.

~~66~~ 60. (New) A method of treating melanoma, non-Hodgkin's lymphoma, multiple myeloma, or Karposi's sarcoma in a patient in need of said treatment which comprises administering to said patient a therapeutically effective amount of a compound of claim ~~59~~ 53.

~~67~~ 61. (New) A pharmaceutical composition comprising the compound of claim ~~59~~ 53 and a pharmaceutically acceptable vehicle or diluent.

THE CLAIMED INVENTION

Claims 1-3, 14, 19-22, and 59 of this application are directed to novel molecules wherein the structure of the 16-member cyclic epothilone ring or substituents attached to the 16-member cyclic epothilone ring are modified. Claims 4, 7-8, 11, 15-18, 23-30, 40-42, 51-58, 60-61, and 63-66 are directed to methods of treating cancer in a patient which comprises administering a therapeutically effective amount of a compound of the invention. Claims 31-38 and 62 are directed to methods of treating cancer responsive to microtubule stabilization which comprises administering a therapeutically effective amount of a compound of the invention. Claims 43-50 and 67 are directed to pharmaceutical compositions comprising a compound of the invention.

Applicants note that the Examiner has previously recognized that claim 3 and 14 are free of the art (*See*, Office Action mailed August 29, 2001, Paper No. 15). Indeed, these claims and those dependent from them have not been rejected over any art in the instant Office Action. Claim 3 is not and has not been dependent from claim 1. Thus, there are *no* rejections pending against claim 3. Further, claim 14 has been amended herein to be in independent form. Thus, no rejection stands against claim 14 or claims dependent therefrom. Applicants respectfully request indication that such claims are allowable.

THE REJECTION UNDER 35 U.S.C. §112,
SECOND PARAGRAPH, SHOULD BE WITHDRAWN

Claims 1-4, 7-8, and 14-58 were rejected under 35 U.S.C. §112, second paragraph, as being indefinite for the reasons set forth on pages 2-3 of the Office Action. The Examiner alleges that the term "substituted" without saying which substituents are intended is indefinite. First, Applicants respectfully traverse this rejection as it is applied to claims 3 and 14 since they do not recite the term "substituted." Thus, the rejection is improper and should be withdrawn.

Applicants respectfully submit that independent claim 1 is not indefinite. "Whether a claim is . . . [indefinite] depends on whether those skilled in the art would understand the scope of the claim when the claim is read in the light of the specification." *North American Vaccine Inc. v. American Cyanamid Co.*, 28 U.S.P.Q.2d 1333, 1339 (Fed. Cir. 1993). Applicants respectfully submit that one of ordinary skill in the art, reading the specification, would readily understand what is meant by the term "substituted." The specification clearly provides a definition for the term "substituted." For example, the term "substituted alkyl" and "substituted aryl" are both defined (*See, e.g.*, Specification, page 4, lines 14-31 and page 5, lines 9-18, respectively). Accordingly, one of ordinary skill in the art, reading the disclosure, would readily understand what scope is meant by the term "substituted."